Risk Factors for Cardiovascular Disease: One Down, Many More To Evaluate

Almost 50 years ago, investigators observed the association between uric acid and cardiovascular events. Subsequently, many epidemiologic studies have sought to clarify the role of this risk factor. In addition, laboratory studies have attempted to identify the mechanism by which an elevated uric acid level causes an increased risk for cardiovascular disease. Despite these efforts, the role of uric acid as a risk factor was never fully resolved.

In this issue, investigators from the Framingham Heart Study resolve the long-standing controversy surrounding the role of uric acid as a risk factor for cardiovascular disease (1). Taking advantage of careful measures and long-term follow-up of a cohort of 6763 Framingham Heart Study participants, Culleton and colleagues found that an elevated uric acid level was strongly associated with a higher age-adjusted risk for coronary heart disease, death from cardiovascular disease, and death from all causes in women but not in men. However, after adjustment for other cardiovascular disease risk factors, such as body mass index, blood pressure (and use of antihypertensive medications), diabetes, cholesterol, smoking, alcohol intake, left ventricular hypertrophy, and menopausal status, they found no association between uric acid levels and any of the outcomes in men or women.

The study is important beyond the resolution of the uric acid controversy. It is another example of the rigorous methods used by the Framingham investigators to expand our knowledge and understanding of risk factors for cardiovascular disease. In the little more than 50 years of its existence, the Framingham Heart Study has yielded many of the central insights that support our current approach to assessing risk for cardiovascular disease. The investigators' high standards have consistently led to observations of enduring value.

Through recent advances in molecular biology and transgenic techniques, laboratory science has identified many potential new risk factors, mostly thrombotic and inflammatory markers of atherogenesis (2–5). The development of new diagnostic methods to detect subclinical disease has also expanded the number of potential risk factors. Because such risk factors are introduced with increasing frequency, the example of the uric acid study is particularly relevant. It is clear that the challenge of evaluating risk factors will increase as the pace of scientific inquiry accelerates.

Enthusiasm for new cardiovascular risk factors needs to be accompanied by efforts to critically evaluate their independent association with the incidence of cardiovascular disease and their practical clinical utility. For many of these new markers, epidemiologic data are still conflicting and clinical utility is still questionable. Will these new markers help to stratify patients by risk, and will they help explain the overall variability in risk? Will they provide targets for intervention? What will be their place in clinical medicine?

As we move forward in our understanding and characterization of cardiovascular disease, sound epidemiologic methods, such as the use of population-based cohorts, adequate sample size, and appropriate control for confounding, remain paramount in the assessment of a valid association between new markers and coronary heart disease. In addition, if a risk factor can be modified, it is important to consider whether modification decreases cardiovascular risk. These fundamental principles of evaluation from the past need to be our guides for the future.

An important challenge is to develop approaches that accelerate our evaluation of proposed risk factors. It is notable that it has taken nearly five decades to definitively assess the role of uric acid. Even established risk factors, such as cholesterol, remain controversial in certain subgroups, such as the very elderly (5, 6). Of the new risk factors proposed in recent years, only C-reactive protein (7–9) and several hemostatic factors (10, 11) have been consistently shown to be independently related to risk for coronary heart disease. For most of the proposed

new risk factors, firm evidence of causality remains elusive.

In the evaluation of these risk factors, we must also ensure the adequate study of various population groups. An important feature of Culleton and colleagues' uric acid study is the approach to sex stratification. The natural history of coronary heart disease differs between women and men, and many risk factors also vary by sex. For example, it has long been recognized that elevated triglyceride and low high-density lipoprotein cholesterol levels confer greater risk for coronary heart disease in women and that elevated total cholesterol and low-density lipoprotein cholesterol levels are associated with increased risk in men (12). Similarly, diabetes is a stronger risk factor in women than in men (13). Many such important insights on differences in risk factors between men and women have resulted from the Framingham Study (14–16). These associations would be obscured if analyses were not stratified according to sex. Similar arguments can be made for the importance of studying other traditionally under-represented groups, such as elderly persons and nonwhite populations.

In the evaluation of the clinical utility of new risk factors, other aspects in addition to association with cardiovascular outcomes should be considered. Relevant issues include the prevalence of the marker, the effect size associated with the marker, the underlying risk of the population in which the marker would be measured, and the cost of the measurement. For example, if the new marker is rare in the population, its attributable risk will be low. As a consequence, screening for the new marker would be likely to have little effect on coronary heart disease prevention, even if the association of the factor with coronary heart disease is strong.

We have progressed substantially since Ancel Keys established the Laboratory of Physiological Hygiene at the University of Minnesota and initiated the first prospective studies of cardiovascular disease (17). His work established that the cause of coronary heart disease is multifactorial, a concept that lead to the use of the term "risk factor" rather than "cause." Although expanded research efforts have resulted in significantly greater knowledge about the atherogenic process and risk for coronary heart disease, much work remains. We must develop approaches that will allow more rapid, rigorous evaluation of these emerging markers. Research efforts based on sound methods will be central in the effort to translate findings from the basic science laboratory into clinically useful risk markers. The experience with uric acid should temper premature enthusiasm toward new risk factors and should calm the temptation to rapidly adopt markers that have not been firmly established as clinically relevant.

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